

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
FLUAZIFOP-P-BUTYL (See note on following page)

Chemical Code # 2186, Tolerance # 411  
SB 950 # 339  
May 20, 2002  
Revised: 5/5/03

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, possible adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	Data gap, inadequate study, possible adverse effect indicated (hamster)
Reproduction, rat:	Data gap, inadequate study, possible adverse effect indicated
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	Data gap, inadequate study, no adverse effect indicated
Neurotoxicity:	Not required at this time

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Toxicology one-liners are attached. This summary also contains sections for metabolism studies and acute toxicity studies (following DNA damage section).

All record numbers for the above study types through 180756 (Document No. 411-125) were examined. This includes all relevant studies indexed by DPR as of 4/29/03.

In the 1-liners below:

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

NOTE: Fluazifop-p-butyl is the R-isomer of the older racemic form, fluazifop-butyl. There are no registered products in California for racemic fluazifop-butyl. The original tolerance number for the racemic product has been retained for the modern purified product. Aldous, 4/8/02.

File name: t20030505.wpd

Revised by: (original by C. Aldous, 5/5/03).

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

### COMBINED, RAT

**\*\*411-0126 201030** Macrae, S. M., "Fluazifop-p-butyl: Final Report: Lifetime feeding study in rats to assess chronic toxicity and potential carcinogenicity," Life Science Research Ltd., Eye, Suffolk, England, 9/2/85. LSR Study No. 82/ILK015/412, CTL Study No. CTL/C/1442, Syngenta No. 8-80. Sixty Wistar rats/sex/group were dosed in diet with PP 009 (fluazifop-butyl), purity 94.8%, for 2 years in a combined chronic/oncogenicity study. An additional 10/sex/group were dosed for 1 year in an interim study. Dose levels were 0, 2, 10, 80, and 250 ppm. Mean estimated exposures were 0.08, 0.41, 3.3, and 10.2 mg/kg/day at increasing dose levels in males, and 0.11, 0.53, 4.3, and 13.4 mg/kg/day in corresponding females. NOEL = 10 ppm, primarily characterized by premature geriatric nephropathy (a "possible adverse effect") and fibrinopurulent bronchopneumonia in males (both findings being reported in nearly all decedents), frequently associated with serum changes such as elevated cholesterol, decreased albumin, and elevated  $\alpha_1$  globulin. Both histopathology findings were also elevated in 250 ppm females. Urinary protein was sharply elevated in the above groups at week 26, coinciding with the timing of major pathology and consistent with the nephropathy. Parathyroid hyperplasia was an apparent secondary effect of kidney pathology: among first year decedents of both sexes, only high dose rats were affected. Other findings suggestive of treatment effects were of small magnitude, or were too low in incidence to consider as important primary effects. There was no tumor response. **Acceptable**, with deficiencies as noted in the review. Aldous, 5/5/03.

411-019 and 020 994252 and 994253: McSheeny, T. W. Macrae, S. M. and Finn, J.P. "IH 773: Potential Toxicity and Oncogenicity in Dietary Administration to Rats for a Period Determined by the Lifespan of Animals, Final Report". Life Science Research Report N0. 81/ISK 005/162 [April 13, 1981]. IH 733, purity 95-98.1%, admixed with the feed at concentrations of 0.1, 0.3, 1.0 or 3.0 mg/kg bodyweight/day and fed to 70 CD (remote Sprague-Dawley origin) rats/sex/group for at least 105 weeks. Ten rats /sex/group were sacrificed at week 51 for histopathology. UNACCEPTABLE. Not upgradeable (No MTD [dose selection not justified]; animal mortality at weeks 28-40 [Bronchopneumonia]). (C. Aldous, 9/4/85).

411-082 69475. Same study as 994252 and 994253.

CHRONIC TOXICITY, RAT  
(See also “COMBINED, RAT”).

CHRONIC TOXICITY, DOG

**\*\*411-083 069476** Virgo, D. M., “Fluazifop-butyl: 55 week oral toxicity study in beagle dogs,” Life Science Research, Stock, Essex, England, 10/15/82. LSR Report No. 81/ILK019/620. Six dogs/sex/group were dosed for 55 weeks with Fluazifop-butyl, 99.6% purity, by gelatin capsules at dose levels of 0, 5, 25, and 125 mg/kg/day in a chronic study. Test article within capsules was dissolved in 0.4 ml/kg corn oil vehicle. NOEL = 5 mg/kg/day. The degree of adrenal gland cortical fatty degeneration evident in one mid-dose female was sufficiently greater than that of any of the control dogs that investigators attributed this finding to treatment. Cortical fatty degeneration of moderate to severe degree was observed in one high dose male and in all high dose females. All other noteworthy findings were limited to the high dose group, as follows. Seven 125 mg/kg/day dogs (5 M, 2 F) were killed *in extremis* prior to term, generally after at least 29 weeks on study. Fluazifop-butyl caused ulcerations in the g.i. tract, specifically in the tongue, lip, mouth lining, stomach pylorus, or cecum. Ulcerations may have contributed to low RBC parameters in both sexes (reduced HCT, Hb levels, and RBC counts, particularly in males). Platelet counts were reduced by about half in both sexes. Bone marrow samples taken at weeks 10 and 52 for smear analyses showed “reduced numbers of megakaryocytes,” suggesting reduced production as a reason for low platelet counts. Other hematology-related findings included increased incidence/degree of thymic involution, decreased lymphocyte counts, increased degree of hemosiderin-laden Kupffer cells, hypercellular sternal marrow, and severe extramedullary hematopoiesis in 4 male and 1 female decedent. Four of the latter 5 dogs also had substantially increased splenic weights, “pallor” in clinical signs as part of moribund condition, and their final hematology red cell values (RBC count, Hb, HCT) were very low. Eyes of eight high dose dogs had cataracts, usually accompanied by miliary (“seed-like” appearance) vacuolation of the lens. Liver dysfunction was indicated by periportal hepatocytic degeneration and thinning of hepatic cords in some dogs, other hepatocytic changes such as vacuolation and/or granular cytoplasm, and occasional bile plugs in the canaliculi. Most clinical chemistry changes were plausibly related to liver toxicity, including elevated alkaline phosphatase, ALT, and occasionally AST. Substantially increased BSP retention was consistent with biliary disturbance. Urine was typically bright yellow or orange due to high bile pigment concentrations. Cholesterol was consistently reduced. Male reproductive toxicity included testicular tubular degeneration and reduced/absent spermatozoa in epididymides. **Possible adverse effects** (many-faceted toxicity, including mortalities, at 125 mg/kg/day). **Acceptable.** Aldous, 5/20/02.

002 3018: One page summary of study 083 69476. Unacceptable. (Apostolou, 9/3/85).

ONCOGENICITY, RAT  
(See also “COMBINED, RAT”).

ONCOGENICITY, MOUSE [OR HAMSTER]

**411-125 180756** Rattray, N. J., "Fluazifop-p-butyl: 80 week carcinogenicity study in hamsters," Central Toxicology Laboratory (CTL), Alderley Park Macclesfield, 2/1/01. Lab Study ID: Syngenta No.1606-01. Golden Syrian hamsters, 51/sex/group, were dosed in diet with 0, 0, 200, 750, or 3000 ppm fluazifop-p-butyl (91.6%) for 81-83 weeks. The dual control groups were treated identically. An additional 12/sex/group (same doses) were allocated for 1-yr sacrifice (for hematology only). Estimated achieved doses were 11.1, 42, and 174 mg/kg/day (M) and 10.6, 40, and 158 mg/kg/day (F) (see next paragraph for explanation for reduction of estimated exposure compared to original year 2002 review). No NOEL was established. Changes seen at all dose levels included chronic progressive nephropathy, factoring both incidence and degree, in kidneys of both sexes; gall stone formation at all dose levels in males; testicular tubular degeneration, factoring both incidence and degree, dose-related in all treated male groups; and elevated liver weights in all female groups. Findings at the higher two dose levels only included decreased testes weights, reduced spermatozoa counts in epididymides and increased cataract development in males. Stromal cell/sex cord hyperplasia was elevated in high dose females. Benign stromal cell/sex cord tumors were slightly but significantly elevated in 3000 ppm females (incidences of 1, 1, 3, 4, and 5 in controls through high dose groups, respectively). Study is not acceptable, but presumed upgradeable (there is a need to explain why this species was selected for this study, and individual data for hamsters should be provided). The ovarian tumor findings, in addition to the several noted histopathology findings without NOEL's, are possible adverse effects. Contemporary historical control data are needed if the registrant desires to re-visit DPR conclusions about findings of this study. The DPR review briefly discusses some ramifications of ovarian and testicular findings. Aldous, 5/20/02, updated 4/29/03 (see paragraph below).

411-0127 201065 Rattray, N. J., "Fluazifop-p-butyl: Final Report: 80 week carcinogenicity study in hamsters," Central Toxicology Laboratory (CTL), Alderley Park, 2/1/01. CTL Study No. PA1097. Syngenta No. 1606-01. A one-volume submission of this study without appendices was previously reviewed as 411-125 180756 (above). The appendices in the present submission do not address the deficiencies noted in the original DPR review. The following change should be noted: mean exposures for increasing dose levels should be corrected to 11.1, 42, and 174 mg/kg/day (M) and 10.6, 40, and 158 mg/kg/day (F) [mean exposures as presented by investigators gave too much weight to the first 13 weeks on study, hence tended to exaggerate mean weekly diet consumption over a lifespan]. The cover letter to the present submission states that hamster pharmacokinetics and metabolism data were to be submitted about June, 2002. These data have not yet been indexed by DPR. Such data alone will not address the issues stated in the 5/20/02 DPR review. Aldous, 4/29/03.

021 994254: McSheeny, T. W. Macrae, S. M. and Finn, J. P. "IH 773: Potential Toxicity and Oncogenicity in Dietary Administration to Mice for a Period Determined by the Lifespan of Animals, Final Report". Life Science Research Report N0. 81/ISK 006/117 [March 9, 1981]. IH 773, purity 95-98.1%, at concentrations of 0.1, 0.3, 1.0 or 3.0 mg/kg bodyweight/day admixed with the feed and fed to 72 Alderley Park mice/sex/group. UNACCEPTABLE. Not upgradeable (too few animals survived to full term [Tyzzler's disease], no MTD). (C. Aldous, 9/5/85).

084 069477. Same study as 994254.

016 994241: Same study as complete report 994254.

011, 12, 16 994250: Summary of 994254.

## REPRODUCTION, RAT

**018 994249:** Tesh, J. M., Willoughby, C. R., Pritchard, A. L. and Whitney, J. C. "Fluazifop-butyl: Effects upon Reproductive Performance of Rats Treated Continuously Throughout Two Generations, Final Report". Life Science Research Report No. 81/ILY 282/130 [March 17, 1981]. Fluazifop-butyl, purity 94.8%, was admixed with the feed at concentrations of 10, 80, or 250 ppm and fed to 2 generations (1 litter/generation) of 15 male and 30 female Wistar rats/group. **Possible adverse effect: Reduced pup survival (number of whole litter losses).** Incidence of hydronephrosis (males only) and organ weight changes were slight and not considered as overt signs of toxicity to adult animals. UNACCEPTABLE. Not upgradeable (dosages not justified; insufficient pup data). (C. Aldous, 8/30/85).

085 69478. Same as 994249.

011, 012, 994247. Summary of 994249

016 994248. Summary of 994249.

## TERATOLOGY, RAT

SUMMARY: Two Life Science Research studies below show that maternal toxicity was minor at 200 mg/kg/day (small reductions in maternal weight in both studies, slightly but statistically significantly elevated relative liver weight in the original study). The later study employed large treatment groups, and is the more definitive study to address effects at associated dose levels. The high dose of 200 mg/kg/day elicited a clear decrease in fetal weight (significant,  $p < 0.001$ ), along with observations such as "small fetuses" and "small placenta." Also, diaphragmatic hernia incidence was remarkably increased in that study (4.4% of fetuses, compared to less than 0.2% in any other groups). Hydronephrosis and hydroureter (unilateral or bilateral) were also elevated at 200 mg/kg/day. Thus the "possible adverse effect" is based on malformations (most definitively diaphragmatic hernia) which cannot be attributed to commensurate maternal toxicity (maternal NOEL = 50 mg/kg/day, NOEL for teratogenicity = 50 mg/kg/day). Ossification delays were marked at this 200 mg/kg/day: examples typical in both studies include bones of the skull, hyoid bone, vertebral centra, sternebrae, metacarpals, and metatarsals. Subtle delays in ossification, particularly in the cranial bones, extended in dose-related fashion to 5 mg/kg/day. Re-examination of the soft tissue data for the original LSR teratology study found no clear dose-responses at 10 or 50 mg/kg/day. In the second study, unilateral hydroureter incidences (% of fetuses) were 2.79, 3.61, 3.91, 4.70, and 8.75% for 0, 1, 5, 10, and 200 mg/kg/day groups. Corresponding bilateral incidences were 1.53, 2.41, 3.91, 4.51, and 16.18%. Investigators considered the findings at 5, 10, and 200 mg/kg/day to represent treatment-related fetal developmental delays. Thus minor developmental delays (delayed ossification and hydroureter) set the developmental toxicity NOEL = 1 mg/kg/day. This appears to be a conservative assessment, and is not based on an "adverse" finding. Aldous, 5/10/02.

**\*\* 018 994245:** Tesh, J. M., Wilby, O.K. and Tesh, S. A. "PP009: Effects of Oral Administration upon Pregnancy in the Rat, Final report". Life Science Research report No. 80/ILK 004/192 [May 23, 1980]. Fluazifop-butyl, purity 94.8%, was administered via gavage at concentrations of 10, 50 or 200 mg/kg to 22 mated female Sprague-Dawley rats/group during

gestation days 6 through 20. Significant increase in diaphragmatic hernia at 200 mg/kg/day is a possible adverse effect. See "Summary" statement at beginning of this section for a consolidated evaluation of this study and the one which follows. Acceptable. (C. Aldous, 8/27/85, 1-liner edited on 5/10/02).

086 69479. Same as 994245.

**\*\* 018 994246:** Tesh, J. M. and Willoughby, C. R. "Fluazifop-butyl: Additional Teratology Study in the Rat". Life Science Research report No. 81/ILK 028/247 [June 3, 1981]. Fluazifop-butyl, purity 94.8%, was administered via gavage at concentrations of 1, 5, 10, or 200 mg/kg to 160 pregnant Sprague-Dawley rats/group during gestation days 6 through 20. Diaphragmatic hernia incidence was sharply elevated at 200 mg/kg/day, a "possible adverse effect". Fetotoxicity NOEL = 1 mg/kg/day (increased incidence of hydronephrosis). See Summary statement at beginning of this section. Acceptable. (C. Aldous, 8/29/85, 1-liner edited 5/10/02).

086 69480. Same as 994246.

#### TERATOLOGY, RABBIT

SUMMARY: Rabbit studies were reported in 1980 and 1993 (below). The latter study (Record No. 135236) was conducted according to current guidelines, and found no evidence of eye defects at 50 mg/kg/day, a maternally toxic dose level. The earlier study (Record No. 994244) had reported "cloudy eyes" in fetuses at 90 mg/kg/day. At that dose level, only 9 does delivered at term, whereas there were 7 abortions and 6 early deaths in that group. It is not clear how many of these losses were due to toxicity and how many were due to management problems. In any case, the more recent study covered an effective dosage range, and justifies an overall conclusion that there are no "adverse effects" evident for rabbit developmental toxicity. Aldous, 5/9/02.

**\*\*411-110 135236** Moxon, M. E., "Fluazifop-p-butyl: Developmental toxicity study in the rabbit," Zeneca Central Toxicology Laboratory, Alderley Park, 3/23/93. Report # CTL/P/3862. Twenty mated NZW rabbits were dosed by gavage in 1 ml/kg corn oil at 0, 2, or 10 mg/kg/day Fluazifop-p-butyl technical (90.1% purity) between days 8 and 20 of gestation (natural mating day was designated "day 1"). There were also 40 mated does given 50 mg/kg/day of test article, to ensure adequate numbers of surviving litters. Maternal toxicity was generally low: mean body weight was unaffected and there were no characteristic clinical signs. There was one maternal death (killed *in extremis*) among the high dose females. Abortion frequencies were 1/18, 2/17, 2/13, and 4/37 in controls through increasing dose groups, thus not independently indicative of treatment effects at any dose. Nevertheless, a combination of marked body weight losses (average loss of 654 g) and associated signs of "few feces" or "no feces" among the 4 of the 5 aborted/killed moribund does is considered treatment-related, setting the maternal NOEL = 10 mg/kg/day. Other maternal and general developmental toxicity indices did not indicate treatment effects, however modest ossification delays (2<sup>nd</sup> and 5<sup>th</sup> sternabrae) and increased incidence of extra 13<sup>th</sup> rib (all at 50 mg/kg/day) placed the developmental toxicity NOEL = 10 mg/kg/day. Acceptable, with no adverse effects. Aldous, 4/17/02.

**018 994244:** Tesh, J. M., Ross, F. W. and Tesh, S. A. "PP009: Effects of Oral Administration upon Pregnancy in the Rabbit, Final report". Life Science Research report No. 80/ILK 027/498 [November 28, 1980]. PP009, purity 94.8%, administered via gavage at concentrations of 10, 30 or 90 mg/kg/day to 20-24 artificially inseminated female New Zealand rabbits during gestation days 6 through 28. **Adverse effects: increased incidence of cloudy eyes (12.7%), small fetuses, delayed ossification and enlarged anterior and posterior fontanelle.** Maternal NOEL = >90 mg/kg/day (no toxicity). UNACCEPTABLE (No MTD, too few pregnant dams at scheduled sacrifice). (C. Aldous, 8/27/85).

086 69481. Same as 994244.

11, 12, 16 994242. Summary of 994244.

### GENE MUTATION

022 994262/35492: Trueman, R.W. "An Examination of PP009 for Potential Carcinogenicity Using Two *In Vitro* Assays". ICI Central Toxicology Laboratory Report No. CTL/P/558 [December 1980]. PP009, purity 94.2-99.6%, was evaluated to determine the potential for carcinogenicity at concentrations of 4, 20, 100, 500 or 2500 : g/plate, with and without metabolic activation and using *Salmonella typhimurium* strains TA 1538, TA100, TA98, TA1535 and TA1537. UNACCEPTABLE. No positive controls without S9 Mix. See DNA section for 35492. (Remsen, 8/29/85).

087 069482. Same study as 994262.

015 994259. Three sentence summary of 994262.

012 994255. Summary of 994262.

016 994260. Summary of 994262 (same as 994255).

**\*\* 30 10482:** Callander, R. D. "PP005: An Evaluation in the *Salmonella* Mutagenicity Assay". ICI Central Toxicology Laboratory Report No. CTL/P/763 [February 1983]. PP005, purity 93.8%, was evaluated to determine the potential for carcinogenicity at concentrations of 0 (DMSO), 1.6, 8.0, 40, 200, 1000 and 5000 : g/plate with and without metabolic activation using *Salmonella typhimurium* strains TA 1538, TA100, TA98, TA1535 and TA1537. Fluazifop-butyl in two assays showed no evidence of a mutagenic response. ACCEPTABLE. (Remsen, 8/29/85).

40 26395. Summary of 10482.

411-039 025297, 411-040 026394 Possibly summaries of Record Nos. 994262, 035492, and/or 010482, above.

87 69483. Same study as 10483.

**\*\* 30 10483:** Callander, R. D. "PP005: An Evaluation in the *Salmonella* Mutagenicity Assay". ICI Central Toxicology Laboratory Report No. CTL/P/765 [November 1982]. Fluazifop-butyl, purity 96.8%, was evaluated to determine the potential for carcinogenicity at concentrations of 0 (DMSO), 1.6, 8.0, 40, 200, 1000 and 5000 : g/plate with and without metabolic activation, using

*Salmonella typhimurium* strains TA 1538, TA100, TA98, TA1535 and TA1537. Fluazifop-butyl in two tests showed no evidence of a mutagenic response. ACCEPTABLE. (Remsen, 8/29/85).

87 69484. Same study as 10483.

40 26395. Summary of 10483.

39 25298. Summary of 10483 (same as 26395).

#### CHROMOSOME EFFECTS

411-098 088830: Bassi, L., R. Pirovano and G. Berruto, "Fluazifop-p-butyl: Chromosome Aberration in Human Lymphocytes Cultured *In Vitro*", Lab Project ID RMB/M813, 4/30/85. Fluazifop-p-butyl was tested at 1, 10, 100, 500, and 1000 : g/ml with and without metabolic activation (S9 Mix) using human lymphocytes to assess chromosomal aberration effects. Purity of test article was not given in the report, but material had an ICI reference number, and contemporary ICI Fluazifop-p-butyl purity was reported in other records to be about 94%. Test article under study conditions did not increase chromosome aberrations. Positive controls were functional. Unacceptable, not upgradeable (fewer than 100 metaphases per concentration without justification). No adverse effects were indicated. (Kishiyama and Aldous, 5/20/02).

\*\* 019 994267: Cuthbert, J. A., Done J. N., McGregor, D.B. and Williams, M. J. "Dominant Lethal Study in Mice of PP009". Inveresk Research International Report No. 1735 [July 1980]. PP009, purity 97.0%, was administered by gavage at concentrations of 0 (corn oil), 28.7, 91.8 or 287.0 mg/kg/day to 15 male and 30 female (Charles River CD-1) mice/group for 5 consecutive days. No increases of dominant lethal effects were observed. ACCEPTABLE (with minor variance: minimal number of females at risks). (C. Aldous, 9/3/85).

087 69487. Same as 994267.

016 994265. Summary of 994267.

016/15 994257. Summary of 994267.

019 994266: Cuthbert, J. A., Done J. N., and McGregor, "Cytogenetic Study in Rats of PP009". Inveresk Research International Report No. 1620 [February 1980]. PP009, purity 94.8%, administered by gavage at concentrations of 0 (corn oil), 21, 67.2 or 210 mg/kg bodyweight to 30 male CD rats/group. Ten animals were sacrificed at 6 and 24 hours after treatment and 10 after 5 consecutive days of dosing. The incidence of chromosomal aberrations did not increase. UNACCEPTABLE. Need justification for testing only males. (C. Aldous, 8/30/85).

087 69486. Same as 994266.

016 994264. Three sentence summary of 994266.

015 994256. Response to 994266.

016/15 994257 Summary of 994266.

30 10481: Phillips, C.E., Richardson, S. R., Burlinson, B. and Styles, J. A. "An Evaluation of PP005 and PP009 in the Mouse Micronucleus Test." ICI Central Toxicology Laboratory Report No. CTL/P/830 [May 1983]. PP009, purity 93.8%, was administered (2 consecutive doses, 24 hours apart) at concentrations of 0 (physiological saline), 250 or 400 mg/kg to 15 C57BL/6J



mice/sex/ to determine the potential for clastogenic activity in the mouse micronucleus test. No evidence of clastogenic activity. UNACCEPTABLE. (no evidence of MTD; only 2 doses; insufficient information). (Remsen, 8/29/85).

411-087 69485. Same study as 10481.

411-040 26395. Summary of 10481.

411-039 25298. Probably a brief summary of 10482 (same as 26395).

#### DNA DAMAGE

022 994262/35492: Trueman, R.W. "An Examination of PP009 for Potential Carcinogenicity Using Two In Vitro Assays." ICI Central Toxicology Laboratory Report No. CTL/P/558 [December 1980]. NOTE: a combined study found with 22 35492. PP009, purity 94.2-99.6%, was evaluated for carcinogenicity potential at concentrations of 0.26, 2.6, 26, 260 or 2600 mg/ml and using BHK-21/C13 (baby Syrian hamster) kidney cells. UNACCEPTABLE. Not upgradeable (No toxicity expressed at highest dose). See Mutagenicity Section for 994262. (Remsen, 8/29/85).

87 69482. Duplicate study of 994242/35492.

016 994261. Summary of 994262.

#### NEUROTOXICITY

Not required at this time.

#### METABOLISM

NOTE: terminology for parent compounds and metabolites varies from study to study. Following are equivalent descriptors:

Fluazifop-butyl = PP009 = the original racemic active ingredient.

Fluazifop-p-butyl = PP005 = R-enantiomer-enriched fluazifop-butyl, which is the current active ingredient.

Fluazifop = PP009 acid (racemic or unspecified as to enantiomers) [compare designations in two reports: Document and Record Nos. 411-031:10924 (Report No. CTL/P/638), p. 2; and Document and Record Nos. 411-031:10923 (Report No. CTL/P/839), p. 3]. This acid is the residue following ester cleavage of the butyl group.

PP004 = R-enantiomer of PP009 acid [see 411-031:10923 (Report No. CTL/P/839), p. 3].

411-002 071079 Brief synopsis of a human oral dosing study. Three male volunteers consumed 0.07 mg/kg/day fluazifop-butyl, followed by evaluation of urine, feces, and plasma. Excretion was 58-81% via urine as fluazifop within the first 24 hr. Between 80 and 93% of dose was recovered in urine within 6 days. Peak blood concentration was found at 1-2.5 hr after dosing. Very little residue was found in feces. Investigators concluded that fluazifop residues in urine provide a meaningful estimate of exposure. Useful summary information, no DPR worksheet. Aldous, 4/24/02.

411-002 003017 Brief synopsis of a spray operator exposure study. Investigators assumed that the disposition of dermally absorbed fluazifop-butyl would be similar to that of orally absorbed material. Analysis of urinary residues after dermal exposure of minimally protected spray operators to urinary residues following oral intake indicated that dermal absorption was less than 1%. Useful summary information, no DPR worksheet. Aldous, 4/24/02.

411-039 025520 This is a summary of several related metabolism studies on fluazifop-butyl and fluazifop-p-butyl. More complete records are found in Document Nos. 411-022 and 411-031 (no DPR review of this summary). Aldous, 4/24/02.

411-031 010925 (Tab Reference 14C) Bratt, H. and I. Moss, "PP009: Excretion and tissue retention of a single intravenous dose (1 mg/kg) in the rat," Report No. CTL/P/611, 7/27/81. <sup>14</sup>C-phenyl-labeled PP009 (racemic fluazifop-butyl) was administered iv to male and female Wistar-derived rats as single 1 mg/kg doses. Excretion was particularly rapid in females, with 84% in urine and 3% in feces within 48 hr. In males, 47% and 11% were found in urine and feces, respectively within 48 hr. An additional 16% and 8% were excreted by males in urine and feces during the next 5 days. Tissue residues were low in males, but much lower in females at day 7 sacrifice. Highest tissue levels were in fat (0.41 and 0.05 : g/g tissue in M and F, respectively, following a single iv dose of 1.0 mg/kg). About 96% of radioactivity in urine or feces of M or F was the acid product of ester cleavage of fluazifop-butyl (henceforth designated "PP009 acid"). Useful supplemental data. No DPR worksheet. Aldous, 5/1/02.

411-022 994281 Same study as Record No. 010925, above.

411-031 010924 (Tab Reference 15C) Batten, P. L. *et al.*, "PP009: Blood level study in the rat," Report No. CTL/P/638, 12/3/81. <sup>14</sup>C-phenyl-labeled PP009 (racemic fluazifop-butyl) was administered iv or by gavage to male and female Wistar-derived rats. Elimination was more rapid in females in all circumstances. Calculated half-lives were: (iv route) 26 hr and 2.7 hr in M and F, respectively, following 1 mg/kg dose, (gavage route for all cases which follow) 33 and 2.7 hr in M and F following 1 mg/kg dose, and 43 and 9.8 hr in M and F following 1 g/kg dose (i.e. clearance was slowed somewhat at high loading doses). Pre-treatment for 14 days at 1 mg/kg/day had no influence on females' elimination rate after a treatment with 1 mg/kg labeled fluazifop-butyl (half-life of 2.6 hr), however half-life for males appeared to be slightly prolonged (38 hr), perhaps due to accumulated loading. Ester hydrolysis was comparatively rapid, and nearly all radiolabel in blood was considered to be PP009 acid: assayed concentration of PP009 acid (: g/ml) in blood was generally very similar to radioactivity expressed as : g equivalents of PP009 acid/ml in blood. Useful supplemental data. No DPR worksheet. Aldous, 5/1/02.

411-031 010923 (Tab Reference 16C) Bratt, H., P. L. Batten, and S. Edwards, "Fluazifop-butyl and PP005: comparative metabolism of a single oral dose (1 mg/kg) in the rat," Report No. CTL/P/839, 7/7/83. <sup>14</sup>C-phenyl-labeled PP009 (racemic fluazifop-butyl) or <sup>14</sup>C-phenyl-labeled PP005 (fluazifop-p-butyl, with enantiomer ratios of 89.4:10.6) were administered along with unlabeled equivalents to Wistar-derived rats, and urine and feces were taken in metabolism cages over time. A few male rats were cannulated to obtain bile samples. Investigators determined that about 90% of urinary radiolabel and over 60% of fecal radiolabel was fluazifop [i.e. PP009 acid]. Two enantiomers of fluazifop exist, one of which was provided in largely purified form (Compound "PP004," fluazifop enriched 87% to 88% in the "R" isomer, the hydrolysis product of PP005). Fluazifop residues were methylated prior to isolation by HPLC or TLC. Only HPLC allowed separation of enantiomers. Isomer quantitation was generally via scintillation counting of eluate fractions corresponding to peaks visualized spectrophotometrically, with unlabeled fluazifop being added to samples if necessary to visualize small peaks (i.e., highlighting the small "S" isomer peak). Disposition of radioactivity following administration of fluazifop-butyl (racemic) or PP005 was essentially identical in males (51% urine/35% feces and 49% urine/35% feces, respectively). Corresponding results in females were 89% urine/3% feces and 75% urine/11% feces, respectively. Subsequently additional females were administered PP005, confirming the relative increase in fecal excretion following treatment with the "R"-enriched isomer. As in other studies, excretion in females was much more rapid than in males. In males provided with biliary cannulae, fluazifop-butyl and PP005 yielded nearly identical percentages of excreted label in bile (42% and 46%, respectively), most of which was collected on days 2 and 3. Tissue concentration after 7 days was highest in fat in either sex, and levels in all tissues were several-fold higher in males than in females (label in most tissues examined was not detectable in females after 7 days). Urine from either males or females dosed with either fluazifop-butyl or PP005 yielded a great predominance of "R" isomer (generally over 95% "R" fluazifop), clearly indicating isomerization within the body. Females favored "R" fluazifop in feces (racemic fluazifop-butyl was converted to about 85% "R" form). In males, fluazifop in feces was substantially "racemized." PP005-derived fecal metabolites averaged 76% "R" fluazifop during days 1-2 collection, and 55% "R" fluazifop during days 3-4 collection. Key conclusions from this study were (1) fluazifop-butyl and fluazifop-p-butyl were both efficiently absorbed following oral dosing (2) fluazifop-butyl and fluazifop-p-butyl were efficiently hydrolyzed and substantially isomerized in the body to the "R" enantiomer of fluazifop, and (3) elimination was very rapid in the urine in females, whereas in males the elimination was slower, with a higher percentage in feces (largely via bile), and (4) tissue residues after 7 days were low in males, and very low in females. Useful supplemental data. No DPR worksheet. Aldous, 5/3/02.

411-031 010922 (Tab Reference 17C) Bratt, H., and P. L. Batten, "Fluazifop-butyl and PP005: comparative blood level study in rats," Report No. CTL/P/967, 12/21/83. <sup>14</sup>C-phenyl-labeled PP009 (racemic fluazifop-butyl) or <sup>14</sup>C-phenyl-labeled PP005 (fluazifop-p-butyl, with enantiomer ratios of 89.4:10.6) were administered by gavage in corn oil to groups of 3 rats/sex/time interval (1, 4, 7, and 12 hr intervals from dosing to blood sampling), to determine blood levels over time and to evaluate R:S enantiomer ratios at each interval. Investigators first confirmed that addition of labeled fluazifop or PP004 to blood *in vitro* had no influence on R:S isomer ratios of fluazifop (the ester hydrolysis product, which accounted for virtually all labeled residues). Male and female rats dosed with either fluazifop-butyl or PP005 had 94% to 99% of

R-fluazifop at each of the 4 time intervals regardless of dosing material. This indicates that the tissue exposure following administration of either racemic or R-isomer-enriched fluazifop-butyl should be equivalent. Useful supplemental data. No DPR worksheet. Aldous, 5/3/02.

411-030 010480 (Tab Reference 9C) "PP 009: Biotransformation in the rat." Report No. CTL/P/654, 8/27/81. This report evaluates identities of major radioactive compounds in urine, feces, bile, and fat in male rats under various dosing regimens with <sup>14</sup>C-labeled PP009. A single large dose (1 g/kg) led to 46% excretion in urine (0-48 hr) and 2% in feces (0-72 hr). Urinary label was 90% PP009 acid. One of the two other residues comprising over 2% of label in urine was the taurine conjugate of PP009 acid. This same taurine product comprised 62% of label in bile (most of the balance of biliary label was PP009 acid: 32% of biliary label). The two rats with biliary cannulae excreted respectively 28% and 48% of administered label in bile. This taurine conjugate comprised only 1% of label in feces, indicating substantial cleavage of the taurine conjugation product in the intestinal lumen. Label in feces was about 52% PP009 acid and 41% unchanged PP009. Fat had been previously shown to have higher levels of radioactivity than other tissues. An analysis in this study showed 54% of label in fat was PP009, and the balance was primarily a conjugate: possibly of a triglyceride. Useful supplemental data. No DPR worksheet. Aldous, 5/8/02.

411-022 994276 Same study as Record No. 010480, above.

411-030 010479 (Tab Reference 10C) "Fluazifop: absorption, excretion and tissue retention of a single oral dose (1.1 mg/kg) in the rat." Report No. CTL/P/663, 10/1981. Three rats/sex were dosed as indicated. Urine and feces were collected, and tissues were collected at day 7 for analysis. Radioactivity in females was found primary in urine (100%) and feces (2%) in the first 48 hr after dosing. Corresponding values in males were 26% and 12% within 48 hr, with an additional 19% and 22% in urine and feces during the following 5 days. Tissue residues at day 7 were below detection in most tissues. Residues in body fat were 0.04 : g/g in females and 0.99 : g/g in males. PP009 acid accounted for 85% to 96% of methanol extracts of urinary and fecal samples of males and females. Small amounts of taurine conjugates of PP009 acid were found in urine or feces (not more than 1.5% in either medium). Investigators concluded that the fate of PP009 acid was very similar to that of PP009, consistent with a rapid hydrolysis of PP009 upon absorption. Useful supplemental data. No DPR worksheet. Aldous, 5/8/02.

411-022 994277 Same study as Record No. 010479, above.

411-030 010478 (Tab Reference 11C) "PP009: Absorption, excretion and tissue retention of a single oral dose (1 mg/kg) in the rat." Report No. CTL/P/568, 6/19/81. Rats were monitored for excreta for 7 days (F) or 10 days (M). Tissues were then taken for radiometric analyses. Some M and F rats were fitted with biliary cannulae, and some were submitted for whole body autoradiography. As in other studies, elimination in F was rapid: 88% of label in urine and 8% in feces within 48 hr. Males excreted 14% and 15% in urine and feces during this period, then 29% and 37% in urine and feces during days 3-10. Cannulated males eliminated 22-45% of label in bile within 2 days, compared to 0.3 to 2% in females. Whole-body autoradiography confirmed the quantities and distribution of residues reported in other studies (highest in body fat in either sex, much higher in M than in F). Parent PP009 accounted for more than half of fecal

residues in M or F, followed by PP009 acid. PP009 acid was by far the predominant metabolite in urine (M and F). No parent PP009 was found in urine. Bile label consisted of 91% PP009-conjugated metabolite (polar, not identified in this report: plausibly taurine, based on other submitted reports) in males. The same metabolite comprised only 17% of label in bile of females. Data suggest that the rather long elimination time in male rats may be related to the degree of conjugation and associated route of elimination that predominates in males. Useful supplemental data. No DPR worksheet. Aldous, 5/8/02.

411-022 994278 Same study as Record No. 010478, above.

411-030 010477 (Tab Reference 12C) "PP009: Absorption, excretion and tissue retention of a single oral dose (1000 mg/kg) in the rat." Report No. CTL/P/610, 8/10/81. Methods and results were similar to the lower dose study above (Record No. 010478). A possibly meaningful difference was that the percentage of male excretion via urinary pathway was comparatively high: (44% of dose in the first 48 hr, and 46% of dose in days 3-7). This might indicate that the biliary excretion of taurine-conjugated residues is saturated at this dose level. Useful supplemental data. No DPR worksheet. Aldous, 5/8/02.

411-022 994279 Same study as Record No. 010477, above.

411-030 010476 (Tab Reference 13C) "PP009: Absorption, excretion and tissue retention following repeated oral administration (1 mg/kg) in the rat." Report No. CTL/P/606, 8/4/81. Rats were dosed with <sup>14</sup>C-phenyl-labeled PP009 (1 mg/kg) following 14 daily treatments with 1 mg/kg unlabeled PP009. Results were comparable to single-dose studies. There does not appear to be anything unique associated with pre-treatment with low amounts of PP009 prior to dosing with labeled test article. Useful supplemental data. No DPR worksheet. Aldous, 5/8/02.

411-022 994280 Same study as Record No. 010476, above.

411-040 026174 Brief summary of metabolism data which had been presented in greater detail elsewhere. No DPR worksheet, Aldous, 5/8/02.

411-011 411-012 , 411-016 994270 Five-page summary of multiple metabolism studies (not reviewable data). Aldous, 5/8/02.

## ACUTE STUDIES

411-031 010921 (Tab Reference 18C) Barber, J. "PP005: Acute oral toxicity, acute dermal toxicity, skin irritation, eye irritation and skin sensitisation of a 25% (w/v) emulsifiable concentrate formulation," Report No. CTL/P/878, Feb. 6, 1984. Test article was GFU 239; Batch Reference 151/10B, with PP005 concentration of 24.7%. Acute oral toxicity study: estimated rat LD50 to be 4.58 ml/kg and >2.3 ml/kg for F and M, respectively. Acute dermal toxicity: LD50 > 2 ml/kg in M and F rats (no deaths, but clinical signs such as "sensitivity to touch, chromodacryorrhea, urinary incontinence, and skin irritation"). Skin irritation results in male rabbits with undiluted material found mean erythema score of 2.11 and mean edema score of 4.00 with undiluted formulation (hence classified as an irritant). Corresponding scores with "spray-strength" (1:40 dilution) were 0.22 and 0.67. All signs were cleared by 3 days, hence "spray-strength" material was classified as a non-irritant. Eye irritation of a spray strength dilution was tested in female rabbits. One rabbit was treated with 0.1 ml, and was observed to have "moderate initial pain." Subsequent tests were done with locally anesthetized rabbits. Eyes of three rabbits were washed 30-60 sec after dosing ("irrigated" group): others were unwashed. Investigators concluded that spray strength dilution was a "mild irritant" in non-irrigated eyes, and a "slight irritant" in irrigated eyes. Guinea pigs were evaluated by the maximization test of Magnusson and Kligman (1970) for skin sensitization. Animals were first given induction treatments intradermally (with a combination of full-strength test article, half-strength test article, and Freund's adjuvant). One week later, scapular areas were treated dermally with undiluted formulation. Corresponding controls received adjuvant intradermally, but distilled water instead of test article in both induction procedures. Two weeks later, the first challenge occurred: undiluted test article on the left flank, and 1:2 dilution on the right. About 2 weeks later, a second challenge followed: undiluted test article on the left flank, and 1:120 dilution on the right. The undiluted emulsifiable concentrate formulation was found to be a moderate sensitizer upon the first challenge, and a strong sensitizer 2 weeks later upon second challenge. The right-flank treatment (1:2 dilution, then 1:120 dilution) achieved a much lesser response, and this was classified as a "weak" sensitization response. Investigators concluded that repeated skin contact "may cause delayed contact hypersensitisation." No DPR worksheet, Aldous, 5/7/02.

411-030 010490 (Tab Reference 1C) "Fluazifop-butyl (racemate): acute oral and acute dermal toxicity studies." Report No. CTL/P/860, 12/1983. Racemic technical fluazifop-butyl had an estimated oral LD50 of 1940 mg/kg in male rats and 2653 mg/kg in females. The dermal LD50 in rabbits was over 2 ml/kg (no deaths at this dose level: diarrhea in 3/10, minimal acute dermal irritation in 3/10). No DPR worksheet, Aldous, 5/7/02.

411-030 010489 (Tab Reference 2C) "R isomer of fluazifop-butyl (PP005): acute oral and acute dermal toxicity studies." Report No. CTL/P/755, 3/13/84. R isomer of technical fluazifop-butyl had an estimated oral LD50 of 3680 mg/kg in male rats and 2451 mg/kg in females. Signs in rats included decreased activity, hunched back, piloerection, urinary incontinence, and stained snout. The dermal LD50 in rabbits was over 1.73 ml/kg (shaved, abraded dorsal skin: occlusive dressing and plastic collars were used to prevent disturbance of the dressing). There were no deaths at this dose level. One of the 10 treated rabbits had diarrhea, and one presented slight evidence of a dermal response. No DPR worksheet, Aldous, 5/7/02.

411-030 010486, 010487, and 010488 (Tab Reference 3C) "PP005: Skin irritation, eye irritation and skin sensitisation." Report No. CTL/P/856, 6/10/83. Rabbits in skin irritation tests received 0.5 ml to the shaved, unabraded left flank. There was very slight to well-defined erythema, and very slight to slight edema on 5/6 animals. Eye irritation tests found very little indication of initial pain at instillation. Minor temporary conjunctival redness, chemosis, and/or discharge occurred in some rabbits. All symptoms disappeared within 2 days. Skin sensitisation: guinea pigs were evaluated by the maximization test of Magnusson and Kligman (1970). Animals were first given induction treatments intradermally (with a combination of 5% test article in corn oil, 5% test article in corn oil with Freund's adjuvant, and Freund's adjuvant:corn oil 1:1). One week later, scapular areas were treated dermally with undiluted test article. Controls received corn oil instead of test article in all cases. The challenge tests began 2 weeks after the dermal induction procedures. Initial challenge was with 75% PP005 in corn oil. Because of marked dermal irritation, rabbits were dosed at 50% and 25% strength PP005 in corn oil, which again revealed irritation. A final challenge with 10% and 25% PP005 in corn oil found no response at 25%, and "scattered mild redness" in one rabbit at 10% PP005. Investigators concluded that PP005 was negative for skin sensitization in this study. No DPR worksheet, Aldous, 5/7/02.

411-030 010485 (Tab Reference 4C) "PP 009: Primary dermal irritation study in rabbits." LSR Report No. 79/ILK8/056, 1/29/79. Two applications of undiluted test article were applied per rabbit to intact skin, and two/rabbit to abraded skin. Rabbits were observed on days 1, 3, and 7 after dosing. All rabbits were observed to have erythema at a minimum of one application site on day 1 or day 3 (very slight to well-defined). All rabbits were clear by day 7. There were no evident clinical signs. Investigators concluded that PP 009 was "mildly irritating" to skin. No DPR worksheet, Aldous, 5/7/02.

411-030 010484 (Tab Reference 5C) "PP 009: dermal sensitization study in guinea-pigs." LSR Report No. 80/ILK026/349, 8/12/80. Male guinea pigs were used throughout. Ten negative controls received no induction treatment, then challenge with undiluted PP009. Ten positive controls received induction treatment with 2% dinitrochlorobenzene (DNCB) in acetone, then challenge with DNCB in sesame oil. Twenty animals received undiluted PP009 for induction and later for challenge. Induction consisted of 10 injections intradermally on alternate days over a 3-wk period (0.05 ml/injection). Challenge was via a single intradermal injection of 0.1 mg/animal at a site not identical to sites previously injected. Skin reactions were assessed 24 and 48 hr after challenge. Undiluted PP009 was found to be non-irritating. PP009 caused either no irritation or occasionally "very slight" irritation during the induction phase. There was no response to the subsequent challenge. Positive controls were very responsive. Thus PP009 was judged as a non-sensitizer. No DPR worksheet, Aldous, 5/7/02.